Original article

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Technetium-99m methoxyisobutylisonitrile scintigraphy in the assessment of cold thyroid nodules: is it time to change the approach to the management of cold thyroid nodules?

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Background **Scanning with technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) is recommended for evaluating thyroid nodule metabolism. In addition, it may help differentiate between benign and malignant nodules; however, the efficacy of this technique has not been fully elucidated. Therefore, it is not currently performed for routine clinical application. This prospective study was conducted to investigate the clinical significance of ^{99m}Tc-MIBI scintigraphy in the assessment of patients with cold thyroid nodules.**

Patients and methods **This prospective study was conducted on 104 patients with cold thyroid nodules greater than 1 cm in diameter as detected on ^{99m}Tc-pertechnetate scintigraphy. Uptake of MIBI in thyroid nodules was compared with that in the surrounding normal thyroid tissue for both early and delayed images, and a score of 0–3 was assigned to each nodule as follows: 0, cold; 1, decreased; 2, equal; 3, increased. The thyroid scan was performed 20 and 40 min after intravenous injection of 555 MBq of ^{99m}Tc-MIBI. The patients underwent fine-needle aspiration cytology (FNAC). Detailed statistical parameters were determined on a per-nodule basis for each qualitative and quantitative scan analysis, as defined by histology.**

Results **A total of 104 patients (93 women and 11 men; mean age 40.76±11.40 years, range 20–73) with a total number of 167 cold nodules were included in this study. When ^{99m}Tc-MIBI uptake was regarded as the criterion of malignancy in ^{99m}Tc-MIBI scintigraphy, the accuracy was between 69.46 and 92.21% on using seven different methods. In addition, FNAC findings indicated a sensitivity of 66.66%, a specificity of 100%, a negative predictive value of 95.72%, a positive predictive value of 100%, and an accuracy of 96.06%. Six malignant cold nodules were detected on a positive ^{99m}Tc-MIBI scan, which were determined as benign nodules on FNAC examinations.**

Conclusion **The study demonstrated that ^{99m}Tc-MIBI scanning can be complementary to other diagnostic techniques in patients with cold thyroid nodules. In addition, because of its availability, rather low cost, simple protocol, and objective semiquantitative information, ^{99m}Tc-MIBI scanning seems to hold promise in routine imaging of cold thyroid nodules.** ***Nucl Med Commun*** **35:51–57 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Thyroid carcinoma is a curable cancer characterized by a nonfunctioning (cold) nodule detected on a technetium pertechnetate scan [1]. Thyroid nodules are quite common, occurring in at least 4–7% of the population [2]. Early and accurate differentiation between malignant and benign nodules can be challenging but is critical to the patient's outcome [1]. Studies have indicated a prevalence of 4–50% for malignancy in thyroid nodules, depending on the surgical indication [3].

Clinical examination gives limited information on the benign or malignant nature of the cold thyroid nodule (CTN). Therefore, other methods such as fine-needle aspiration cytology (FNAC) and ultrasonography are recommended to obtain further diagnostic information [4–6]. Although there are regional differences in the method of choice for initial evaluation, it is generally accepted that, along with laboratory thyroid function tests, FNAC should be the first procedure to be performed. Our previous study revealed that the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of FNAC were 53.84, 98.01, 82.35, 92.50, and 81.81%, respectively [7]. However, with a published sensitivity of 68–98% (mean 83%) and a specificity of 72–100% (mean

92%), FNAC does not seem to be a perfect diagnostic test for the evaluation of thyroid nodules [7,8].

In this respect, a number of scintigraphic modalities such as ^{131}I, ^{123}I, ^{99m}Tc, ^{201}Tl, technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI), and ^{18}F-fluorodeoxyglucose have been assessed for the scintigraphic recognition of malignant nodules [4,5,9]. The majority of such studies have used ^{99m}Tc-MIBI to evaluate thyroid nodule metabolism. The intensity and/or time course of uptake are used for the differentiation of benign from malignant nodules. However, the published results are not consensual [10–13]. The procedure offers high patient acceptability, low cost, easy protocol, and good image quality. However, the efficacy of the ^{99m}Tc-MIBI scan in this issue is not fully elucidated. As such, the aim of this prospective study was to investigate the clinical significance of ^{99m}Tc-MIBI scintigraphy in the assessment of patients with CTNs. The results of this modality were compared with the histological diagnosis of the thyroidectomy specimen as the reference (gold) standard for the presence or absence of malignancy (thyroid cancer). In addition, we had two other objectives: (a) whenever possible, compare this modality with FNAC; and (b) assess the feasibility of this radiotracer for routine practice.

Patients and methods

In total, 104 patients with at least one cold nodule on previous ^{99m}Tc-pertechnetate scintigraphy were included in the study conducted between May 2011 and April 2013. Patients with previous thyroid surgery, known malignant disease, or nonpalpable thyroid nodules smaller than 1 cm in diameter were excluded. In addition, pregnant and nursing women, as well as children (under 14 years old), were also excluded. Besides ^{99m}Tc-pertechnetate scintigraphy, all 104 patients had previously undergone an ultrasound examination, FNAC, thyroid hormone measurements (sensitive TSH, free thyroxine), and ^{99m}Tc-MIBI thyroid scans, and all had previously been selected for surgery on the basis of their clinical and paraclinical findings.

The study complies with the declaration of Helsinki and was approved by the institutional ethics committee of Bushehr University of Medical Sciences; all patients gave written informed consent.

Fine-needle aspiration cytology

FNAC was performed by experts using the suction technique and a 23-G needle. Between three and four samples were obtained from different nodule areas. The samples were smeared on at least four glass slides, two for air-drying and two for fixation in methanol. Dry smears were stained by Wright–Giemsa and methanol-fixed smears were stained by Papanicolaou. All samples were assessed by expert thyroid gland pathologists, and the results were reported by consensus according to the classification of the American Association of Clinical Endocrinologists Consensus for the study of thyroid nodules [14] as follows: (a) nondiagnostic, (b) benign (non-neoplastic), (c) follicular lesion/neoplasm, (d) suspicious, (e) or positive for malignant cells.

^{99m}Tc-MIBI scans

Two MIBI thyroid scans were obtained for each patient. Early MIBI thyroid scans were obtained 20 min after intravenous administration of 555 MBq of ^{99m}Tc-MIBI. A second (late) set of MIBI scans was obtained under the same conditions, 40 min after intravenous administration of MIBI. All scans were obtained for the anterior projection of the neck with a double-detector gamma camera (ADAC Genesys, Malpitas, California, USA) equipped with a general-purpose parallel-hole, low-energy collimator. Images were obtained in a 128×128 matrix using a digital zoom of 2.

The acquisition time for both (early and late) images was set at 5 min with a 20% window centered at 140 keV in all cases. For ^{99m}Tc-MIBI scintigraphy, as had been used in prior studies [15], accumulation of the tracer in the nodules was visually scored and semiquantitative analysis was performed. Images were assessed by two nuclear medicine physicians and discrepant results were resolved by consensus.

^{99m}Tc-MIBI uptake in the nodules for both early and delayed images was scored as follows: score 0 (cold), no significant uptake; score 1 (decreased), uptake increased as compared with background activity, but lower than that in normal thyroid tissue; score 2 (equal), uptake equal to that in normal thyroid tissue; and score 3 (increased), uptake exceeding that in normal thyroid tissue. Semiquantitative analysis was performed using a lesion to nonlesion ratio on early (ER) and delayed images (DR) after background correction. A circular region of interest was generated over the area of the thyroid nodule. For background, circular regions of interest were drawn three pixels below the normal lobe of the gland. In addition, a retention index (RI) was calculated using the formula:

$$\mathrm{RI} = (\mathrm{DR}-\mathrm{ER}) \times 100/\mathrm{ER}.$$

Seven methods for the differential diagnosis of thyroid nodules on ^{99m}Tc-MIBI scintigraphy were studied. In method 1, a lesion scored 2 or 3 in the early image was considered malignant; in method 2, a lesion scored 2 or 3 in the delayed image was considered malignant; in method 3, a lesion scored 3 in the early image was considered malignant; in method 4, a lesion scored 3 in the delayed image was considered malignant; in method 5, a lesion scored 2 or 3 in the early or delayed images was considered malignant; in method 6, a lesion scored 3 in the early or delayed images was considered malignant; in method 7, a lesion scored 3 on both early and delayed images was considered malignant. These data were compared with the results of histopathological studies.

Statistical analysis

The distribution of variables was assessed using probability plots and the Shapiro–Wilk test. Continuous variables are expressed as mean ± SD and categorical variables as absolute values and percentages. A two-tailed *t*-test was used to compare the mean values between the groups. The sensitivity, specificity, accuracy, and positive and NPVs of each imaging method were obtained on the basis of the definitive diagnosis established through histopathology. A receiver operating characteristic (ROC) curve analysis was performed to determine ER, DR, and RI threshold levels for the differentiation of malignant from benign nodules. The results were considered statistically significant when the P value was less than 0.05. Statistical analysis was performed using an IBM computer (Armonk, New York, USA) and PASW software, version 18.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 104 patients (93 women and 11 men; mean age 40.76 ± 11.40 years, range 20–73) were included in this study. The total number of cold nodules was 167: one nodule in 72 patients, two nodules in 20 patients, three nodules in five patients, and four nodules in 10 patients. Seven patients were identified as having a suspicious/follicular neoplasm on FNAC, which were revealed as being benign on surgery and histopathology. Histological findings were malignant in 14 patients (all cases of papillary carcinoma) and benign in 90 patients (Table 1). The mean size of malignant tissue was 5.5 mm (range: 3–13 mm).

Table 1 Histopathology of cold thyroid nodules

Histopathology of nodules	Frequency (%)
Nodular goiter	99 (59.3)
Colloid goiter	23 (13.8)
Adenomatous goiter	17 (10.2)
Follicular adenoma/neoplasia	4 (2.4)
Multinodular goiter with cystic changes	2 (1.2)
Adenomatous goiter with Hurtle cell changes	3 (1.8)
Nodular hyperplasia with hyperplasia and lymphocytic infiltration	4 (2.4)
Papillary cell carcinoma	15 (9.0)
Total	167 (100)

Predictive value of ^{99m}Tc-MIBI for thyroid malignancy compared with FNAC

When ^{99m}Tc-MIBI uptake was regarded as the criterion for malignancy in ^{99m}Tc-MIBI scintigraphy, the accuracy was between 69.46 and 92.21% on seven different methods (Figs 1 and 2). On a comparison between these seven methods, method 2 (scored 2 or 3 in the delayed image) demonstrated the most reasonable detection rate in the diagnosis of malignant cold nodules with a sensitivity of 100%, specificity of 78.29%, NPV of 100%, PPV of 31.25%, accuracy of 80.23%, positive likelihood ratio of 0.45, and negative likelihood ratio of 0. The detailed statistical parameters are noted in Table 2.

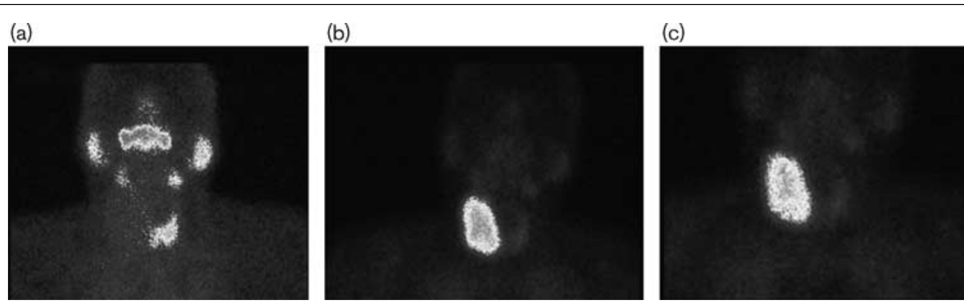
In addition, only 10 of 15 malignant cold nodules showed increased uptake (score 3) in the early or delayed views; the five remaining malignant cold nodules showed equal activity (score 2) in the scans. In addition, patients with suspicious or follicular neoplasm (class 3 or 4) based on FNAC showed different patterns of uptake (Table 3).

Overall, FNAC findings indicated a sensitivity of 66.66%, a specificity of 100%, an NPV of 95.72%, a PPV of 100%, and an accuracy of 96.06%. Histopathology revealed six malignant cold nodules, which were considered as benign nodules on FNAC. All such nodules showed uptake on ^{99m}Tc-MIBI scintigraphy.

Semiquantitative analysis of malignant and benign nodules

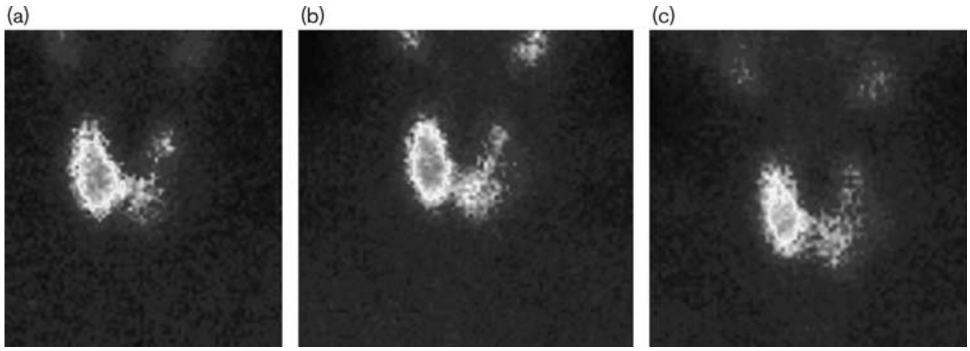
In semiquantitative analysis, ^{99m}Tc-MIBI uptake values were higher in malignant nodules than in benign nodules ($P < 0.05$), either in the ER (mean value 1.23 ± 0.69 vs. 0.61 ± 0.50) or in the DR (mean value 1.49 ± 0.70% vs. 0.59 ± 0.41). In addition, the RI value demonstrated more activity in malignant nodules than in benign nodules

Fig. 1



(a) ^{99m}Tc-pertechnetate scintigraphy in a 42-year-old man with a cold nodule on the right lobe of the thyroid gland. (b, c) Significant ^{99m}Tc-MIBI activity in the right side of the thyroid gland after 20 min (b) and 40 min (c). The lesion to nonlesion ratio on early views is 3.59 and that on delayed images is 3.60. Two fine-needle aspiration cytology findings showed a nodular goiter but histopathology examination showed a papillary cancer of 5 mm diameter.

Fig. 2



(a) ^{99m}Tc-pertechnetate scintigraphy in a 35-year-old woman with a cold nodule on the left lobe of the thyroid gland. (b, c) No ^{99m}Tc-MIBI activity in the left side of the thyroid gland after 20 min (b) and 40 min (c). The lesion to nonlesion ratio on early views is 0.20 and that on delayed images is 0.24. FNAC and histopathology examination findings showed a nodular goiter.

Table 2 Comparison of statistical parameters in different methods of ^{99m}Tc-MIBI scintigraphy and fine-needle aspiration cytology

Method	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)	Positive likelihood ratio	Negative likelihood ratio
1	100	67.10	100	23.07	70.05	0.3	0
2	100	78.29	100	31.25	80.23	0.45	0
3	66.66	94.07	96.62	52.63	91.61	1.11	0.03
4	66.66	93.42	96.59	50	85.62	1	0.03
5	100	66.44	100	22.72	69.46	0.29	0
6	66.66	92.76	96.57	47.61	90.41	0.90	0.03
7	66.66	94.73	96.64	55.55	92.21	1.25	0.03
FNAC	66.66	100	95.72	100	96.06	ω	0.04

Method 1, a lesion scored 2 or 3 in the early image was considered malignant; method 2, a lesion scored 2 or 3 in the delayed image was considered malignant.; method 3, a lesion scored 3 in the early image was considered malignant; method 4, a lesion scored 3 in the delayed image was considered malignant; method 5, a lesion scored 2 or 3 in the early or delayed images was considered malignant; method 6, a lesion scored 3 in the early or delayed images was considered malignant; method 7, a lesion scored 3 on both early and delayed images was considered malignant.
FNAC, fine-needle aspiration cytology.

Table 3 Tc-MIBI uptake in patients with suspicious/follicular and malignant nodules based on fine-needle aspiration cytology

	Suspicious/follicular		Malignant	
Uptake	Early	Delayed	Early	Delayed
0 (no uptake)	2	3	0	0
1 (decreased activity)	2	2	0	0
2 (equal activity)	3	2	5	5
3 (increased activity)	0	0	10	10

(mean value; 0.29 ± 0.16 vs. 0.00 ± 0.22, $P < 0.05$). Furthermore, a significant difference was noted between the ER and DR of the ^{99m}Tc-MIBI scan in malignant nodules (mean value 1.23 ± 0.69 vs. 1.49 ± 0.70, $P < 0.05$). Similarly, such a difference was observed in benign nodules (mean value 0.62 ± 0.50 vs. 0.59 ± 0.41, $P < 0.05$).

To determine the predictive value of ^{99m}Tc-MIBI uptake for the final outcome of each thyroid nodule, an ROC curve analysis was performed separately for three values. The area under the ROC curve was 0.882 ± 0.03 ($P < 0.000$) for the ER, 0.911 ± 0.03 ($P < 0.000$) for the DR, and 0.826 ± 0.052 ($P < 0.000$) for the RI. Furthermore, considering the optimal cutoff point for ER as 0.80, for DR as 0.11, and for RI as 0.16, the sensitivity and specificity were calculated as 93.3 and 73% for ER, 93.3 and 74% for DR, and 80 and 79% for RI, respectively (Fig. 3).

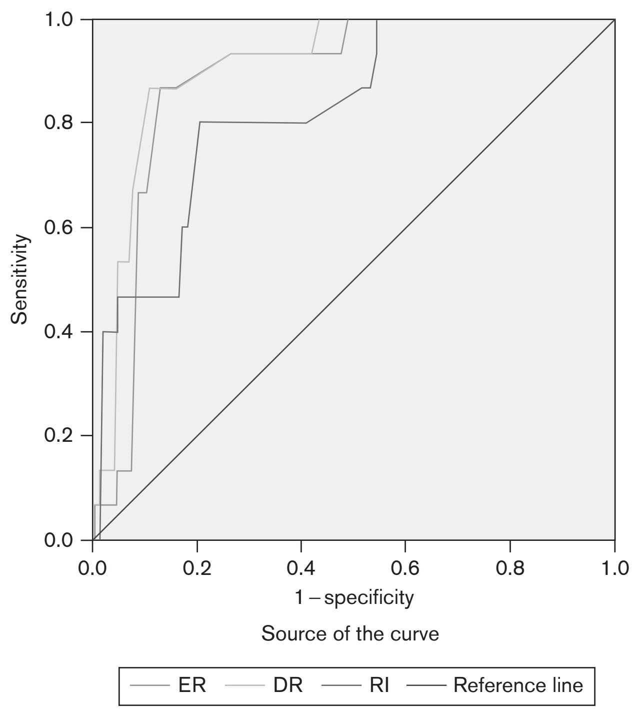
Discussion

Nodular disease of the thyroid gland is one of the most frequent problems in endocrinology, and the optimum diagnostic and therapeutic strategy for patients with CTNs is still a matter of debate [15]. Currently, thyroid FNAC is indicated as a critical test for the management of thyroid nodules. However, standard FNAC is non-diagnostic in 25–40% of cases, which include inadequate specimens and indeterminate (suspicious) diagnoses [16]. Several imaging modalities such as ultrasound and scintigraphy are also recommended for the evaluation of thyroid nodules [17,18].

Thyroid ultrasonography is helpful as a guide for FNAC, to confirm the presence of a mass and its relation to the thyroid, and to assess the size or the number of thyroid nodules. However, this technique is not capable of distinguishing between benign and malignant nodules [18,19].

Published reports assessing thyroid nodules with various radiotracers (e.g. ^{201}Tl, ^{99m}Tc-MIBI, tetrofosmin,

Fig. 3



Receiver operating characteristic curve analysis for the prediction of malignant thyroid nodules based on ^{99m}Tc-MIBI uptake values. DR, ratio on delayed views; ER, ratio on early views; RI, retention index.

^{18}F-fluorodeoxyglucose) have not been able to clearly differentiate between benign and malignant thyroid nodules [11,20]. Ascertainment of the radiotracer uptake, analysis of higher uptake relative to the surrounding tissue, and assessment of dynamic changes in uptake (difference between early and delayed scans) are all attempted to differentiate between benign and malignant thyroid nodules [21–23].

In this respect, ^{99m}Tc-MIBI scans of the thyroid have been studied by several groups searching for differences between benign and malignant CTNs. Both semiquantitative methods (i.e. index calculation, washout rate calculation, uptake differences between early and late images, etc.) and visual methods have been used to assess the CTN [13,23]. However, the published information conveys the general idea that MIBI scans are not sufficient for definitive preoperative differentiation between the benign and malignant nature of a CTN [11,23].

The present study was undertaken to evaluate the efficacy of FNAC and ^{99m}Tc-MIBI scintigraphy to determine thyroid cancer in patients with cold thyroid nodules. The question posed was whether ^{99m}Tc-MIBI scintigraphy could be applied in patients with cold nodules. This study depicted its merit in routine management for identifying thyroid cancer in such patients.

The results of this study suggest that a lack of uptake in a cold thyroid nodule on ^{99m}Tc-MIBI scintigraphy is indicative of a benign process, although the presence of uptake in a cold nodule is not necessarily a sign of malignancy. This finding is in line with a number of studies that have documented a complete exclusion of malignant processes in cold thyroid nodules without any activity on ^{99m}Tc-MIBI scintigraphy.

In this study, different levels of activity were observed in the early and late MIBI scans. When a nodule with equal or increased uptake (score 2 or 3) in delayed views was considered a malignant lesion, the scan provided 100% sensitivity and an NPV of 100% in discriminating benign from malignant cold nodules.

In this study, a negative MIBI scan indicated a benign etiology in all patients. Therefore, when the MIBI scan is negative, in the absence of other indications (e.g. cosmetics, obstruction), invasive diagnostic procedures and/or surgery should be avoided.

The PPV of the MIBI scan improved from 22.72% [when a nodule with equal or increased uptake (score 2 or 3) in early or delayed views was considered a malignant lesion] to 55.55% [when a nodule with increased uptake (score 3) in early and delayed views was considered a malignant lesion]. Positive MIBI scans were indeed indeterminate or non-diagnostic. Most patients with a positive MIBI scan had benign cold nodules, as did all patients with a final histological diagnosis of malignancy. Similarly, the probability of a nodule showing uptake on ^{99m}Tc-MIBI scintigraphy divided by the probability of a nodule not showing uptake (positive likelihood ratio) was 0.29–1.25 in different methods.

Furthermore, score 2 was found in benign and malignant CTNs; therefore, mere consideration of score 3 was not suitable for differential diagnosis of malignant from benign nodules. In addition, our results show that each of the two tested diagnostic methods (FNAC and MIBI scans) is independent and gives different complementary diagnostic information. Similarly, this study shows that the combined use of FNAC and MIBI scans provides the best diagnostic accuracy in the study of CTNs. In other words, the ^{99m}Tc-MIBI scan and FNAC are complementary rather than competitive methods.

In agreement with previous studies, differentiated thyroid cancer (DTC) was never identified as a cold nodule on MIBI scans [10,20,23,24]. Hurtado-Lopez *et al.* [13] reviewed 13 published papers in which MIBI was used for the evaluation of patients with CTNs. Of the 448 patients, 127 (28.34%) had DTC, four (0.9%) had medullary cancer, 314 (70.08%) had benign thyroid disease, and three (0.66%) had anaplastic thyroid cancer [13]. All 131 patients with DTC and medullary cancer (127 and four patients, respectively) showed MIBI uptake within the CTN. In the 314 patients with benign disease, MIBI scans were positive in 212 (67.5%) and negative in 102 (32.5%). MIBI scans were positive in only one of the three patients with anaplastic carcinoma [13]. The reviewed data show that the NPV of a negative MIBI scan is 100%.

On semiquantitative analysis, this study demonstrates that the delayed-view parameters are superior to those of early scans for the differentiation of malignant from benign thyroid nodules. Our findings were in agreement with those of Erdil *et al.* [10] who found that malignant thyroid nodules showed higher uptake of ^{99m}Tc-MIBI, especially in delayed images. In addition, the ER, DR, and RI values were higher in malignant nodules than in cold nodules. However, the lesion to nonlesion ratio may vary depending on the imaging techniques, the equipment used, or the patient population. Therefore, each laboratory is advised to establish its own threshold based on a large series of patients.

The thyroid uptake of MIBI depends on the number of mitochondria and the potential of plasma and mitochondrial membranes, because MIBI is held inside the mitochondria [24]. Malignant cells in particular maintain a more negative mitochondrial transmembrane potential and, subsequently, encourage increased MIBI accumulation because of their increased metabolic needs [24].

^{99m}Tc-MIBI is the most common myocardial perfusion scanning agent in all nuclear medicine centers and is available more readily than the aforementioned radiotracers; further, it can be routinely used in thyroid cold nodule evaluation.

In summary, this study confirms that the post-test likelihood for cancer in the setting of a negative MIBI scan is 0% and a negative MIBI scan excludes DTC cancer in all patients with CTN (NPV, 100%). We may suggest a combination of fine-needle aspiration biopsy and MIBI scan as a routine diagnostic approach to CTNs.

Although our study demonstrates good insight into the application of ^{99m} Tc-MIBI as compared with histopathology as the reference in the assessment of cold thyroid nodules, it should be noted that it has some shortcomings. The major limitations are the exclusion of patients with thyroid nodules smaller than 1 cm in diameter because of the limited resolution of current gamma cameras and the presence of papillary thyroid cancer and absence of other types of thyroid cancers, both of which may have influenced the results of this study; therefore, such deficiencies should be considered in further studies. In addition, we did not use pinhole collimators or a SPECT/CT camera, which may be useful, especially for small nodules.

Conclusion

In this study, on the basis of the amount of activity in the early and late MIBI scans, seven methods were assessed. When a nodule with equal or increased uptake (score 2 or 3) in delayed views was considered a malignant lesion (method 2), the scan provided 100% sensitivity and an NPV of 100% in the discrimination of benign from malignant cold nodules. Therefore, it can be complementary to other diagnostic techniques in patients with cold thyroid nodules. In addition, because of its availability, relative low cost, easy performance, and objective semiquantitative data, ^{99m}Tc-MIBI scanning might be established in routine imaging centers to assess cold thyroid nodules; however, further study is needed to validate its clinical role.

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Conflicts of interest

There are no conflicts of interest.

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